International Journal of Celiac Disease, 2014, Vol. 2, No. 1, 31-32
Available online at http://pubs.sciepub.com/ijcd/2/1/9

DOI:10.12691/ijcd-2-1-9

Celiac Disease after the Diagnosis: What We Expect and What Happens in the Reality

Julia Gorgun[1,*], Anna Portyanko[2]

[1]Department of Gastroenterology and Nutrition, Belarusian Academy of Postgraduate Education, Minsk, Belarus
[2]Department of Pathology, Belarusian State Medical University, Minsk, Belarus
*Corresponding author: julia.gorgun@mail.ru

Gluten-dependency of clinical manifestations, serological and histological abnormalities is the key feature of celiac disease (CD) [1]. That means, that in most CD patients, all symptoms as well as mucosal atrophy are potentially reversible after gluten exclusion and based on this fact, gluten-free diet (GFD) is the main treatment option. Classical conception of CD could be described as presence of symptoms, serological CD-markers and intestinal mucosa atrophy which resolve on GFD and reappear after renewal of gluten intake or continue to exist in patients on a gluten-contained diet being in association with life-threatening complications such as refractory CD, T-cell lymphoma, collagenous sprue, bowel adenocarcinoma and other tumors or autoimmune diseases [2]. Prevention of these complications and symptoms requires a life-long GFD. However, gaining more experience in CD brings more and more knowledge about the variability of presentation and course of the disease and changes our approaches to the CD management [3,4]. One part of these changes concerns the process of CD diagnosis and the other one should refer to the CD management after the diagnosis.

At present, there is no unified position concerning details of follow-up of CD patients. According to the revised ESPGHAN criteria, the second biopsy after the period of GFD is not needed any more in most cases, as positive serological tests and symptomatic response allow to diagnose CD definitely [3]. It should be noted, however, that repeated biopsies not only add confidence in the diagnosis of CD but also show the condition of the intestinal mucosa which is the important predictor of the complications development [5,6]. It is known that clinical response to a GFD is evident long before the histological one and can be seen within two weeks after starting a GFD [7]. Histological recovery takes much more time and can last in adults 5 years or ever longer [8]. In initially symptomatic patients, however, the level of GFD strictness needed to relieve bothersome symptoms can be lower than that one needed to repair the intestinal mucosa and to stop the progression of disease. In our cohort of 40 adult CD patients histological remission defined as absence of mucosal atrophy was dependent on a strict GFD with odds ratio (OR) 8,0 (95 % CI 2,89 – 22,2) but OR for having clinical remission on a strict GFD versus no or non-strict GFD was 2,58 (95 % CI 1,25 – 5,31). In this cohort there was no association between clinical response and histological remission and mucosal atrophy persisted in every fifth patient whose symptoms had disappeared. In Kaplan-Meier model, in patients on a strict GFD the possibility of clinical remission 2 years after diagnosis counted 92 % and histological remission – 70 %. In patients non fully compliant with GFD the possibility of asymptomatic state was still high enough and reached 60 % while the possibility of histological remission amounted to 20 % only [9]. Other investigators also point to the significant relationship between the adherence to a GFD and mucosal recovery and poor correlation between clinical symptoms and presence of villous atrophy [9,10]. So the absence of symptoms does not necessarily mean the absence of atrophy.

An important point that we should not forget is that GFD is difficult to follow and it can have a negative effect on patients' social life and quality of life precluding them from full compliance [12,13]. The data about adherence to a GFD are quite variable. For example, in some cohorts self-reported compliance with a GFD is high enough and reaches 79-88 % [9,13]. According to the other data, based on dieticians' assessment, only 42 % of CD patients are adherent to the a strict GFD with 28 % committing moderate transgressions and 29 % - the large ones [15]. Adherence to a GFD can be higher in patients diagnosed in early childhood [16] or in CD revealed due to typical symptoms versus screening-detected CD [17]. The last fact confirms that having symptoms is an important motivation for keeping a GFD and that asymptomatic state can weaken this motivation and "encourage" dietary transgressions. Meanwhile, our tools to control the adherence to a GFD are imperfect. Assessment of food diary requires an experienced dietician, it is time-consuming and patient-dependent and can be false-negative due to intentional or incidental incomplete registration of the ingested food or absence of detailed information about food ingredients. Serological tests are also not sensitive enough and are poor predictors of dietary transgressions [18]. In the study by Sugai N. et al. analyzing 7 CD serologic tests on their ability to distinguish patients strictly and partially compliant with GFD, the best performance showed IgA antitransglutaminase antibodies assay (IgA-tTG-ab) with the area under ROC curve 0.72, sensitivity 76.5 %, specificity 50.0 %, positive and negative predictive value 53.1 % and 74.2 % respectively [19]. According to the data provided by Vahedi K. et al., the proportion of correct recognition of overall, moderate, and large levels of transgressions was 0.52, 0.31, and 0.77 respectively for IgA-tTG-ab, and 0.62, 0.37, and 0.86 for IgA

antiendomysium (IgA-EMA) antibodies [15]. Serological markers also fail to predict histological recovery of intestinal mucosa after starting a GFD and can be negative in both non-compliant and compliant patients despite the persistence of mucosal atrophy, which carries a risk of subsequent severe complications, even in the absence of symptoms and serological CD markers [10,12].

An intriguing side of the real CD course after starting a GFD is a possibility of mucosal recovery in spite of incomplete adherence to a GFD or development of gluten tolerance after a period of a GFD. According to some reports, about 10 % of CD patients diagnosed in childhood remain symptom free and save normal duodenal mucosa after gluten reintroduction showing long-term CD latency [11,20,21]. These patients do not differ from those ones being on a strict GFD in terms of clinical symptoms, nutritional status or presence of non-CD serum autoantibodies, but they are more frequently positive for CD-specific antibodies. Clinical and histological relapse is possible in some of them after a tolerance period lasting some years but in the others, CD remains latent for the long period of time reaching up to 30 years [11]. Mechanisms of this CD latency are unclear and different factors such as genetic [21,22], age of diagnosis [11], continuous ingestion of small doses of gluten in childhood and/or the use of dapsone [23] are supposed to be involved. Descriptions of different scenarios of CD course after diagnosis raise a question whether "transient CD" with full restoration of gluten tolerance really exists or all the variability we see is due to the natural disease history with alternating increase and decrease in gluten tolerance driven by some external, dietary, stress or perhaps infectious factors [11]. The answer to this question as well as exploration of the factors provoking and preventing CD activation is an important prerequisite for the successful long-term management of CD.

In conclusion, there are a lot of unsolved problems concerning the course of CD after diagnosis including the detection of the optimal methods and terms for monitoring the response to a GFD, assessment of compliance with GFD, clarification of the possibility of the development of gluten tolerance and consumption of gluten without increasing the risk of CD complications. There is a need for the long-term follow-up CD studies involving the assessment of histological, immunological, genetic, dietary and other factors which could be potentially involved in reflection and regulation of gluten tolerance in CD patients.

References

[1] Troncone, R., Jabri, B., "Coeliac disease and gluten sensitivity.," *J. Intern. Med.*, 269(6), 582-590, Jun 2011.

[2] Green, P.H., Cellier, C., "Celiac disease," *N Engl J Med*, 357(17), 1731-1743, Oct 2007.

[3] "Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition," *Arch. Dis. Child.*, 65(8), 909-911, Aug 1990.

[4] Ludvigsson, J., Leffler, D., Bai, J., Biagi, F., "The Oslo definitions for coeliac disease and related terms," *Gut*, 62(1), 43-52, Jan 2013.

[5] Kaukinen, K., Peräaho, M., Lindfors, K., Partanen, J., Woolley, N., Pikkarainen, P, Karvonen, A-L., Laasanen, T., Sievänen, H., Mäki, M., Collin, P., "Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease.", *Aliment. Pharmacol. Ther.*, 25(10), 1237-1245, May 2007.

[6] Lebwohl, B., Granath, F., Ekbom, A., Smedby, K., Murray, J., Neugut, A., Green, P., Ludvigsson, J., "Mucosal Healing and Risk for Lymphoproliferative Malignancy in Celiac Disease: a population-based cohort study" *Ann Intern Med.*, 159(3), 169-176, Aug 2013.

[7] Pink IJ, C.B., "Response to a gluten-free diet of patients with the coeliac syndrome.," *Lancet*, 1(7485), 300-304, Feb 1967.

[8] Wahab, P.J., Meijer, J.W., Mulder, C.J., "Histologic follow-up of people with celiac disease on a gluten-free diet: slow and incomplete recovery," *Am J Clin Pathol*, 118(3), 459-463, Sep 2002.

[9] Gorgun, J.V., "Celiac disease in adults: diagnosis, clinical and molecular-genetic characteristic" (Doctoral dissertation), Minsk, BelMAPE, 2012.

[10] Hutchinson, J.M., West, N.P., Robins, G.G., Howdle, P.D., "Long-term histological follow-up of people with coeliac disease in a UK teaching hospital," *Qjm*, 103(7), 511-517, Jul 2010.

[11] Matysiak-Budnik, T., Malamut, G., de Serre, N.P.-M., Grosdidier, E., Seguier, S., Brousse, N., Caillat-Zucman, S., Cerf-Bensussan, N., Schmitz, J., Cellier, C., "Long-term follow-up of 61 coeliac patients diagnosed in childhood: evolution toward latency is possible on a normal diet.," *Gut*, 56(10), 1379-1386, Oct 2007.

[12] Zarkadas, M., Cranney, A., Case, S., Molloy, M., Switzer, C., Graham, I.D., Butzner, J.D., Rashid, M., Warren, R.E., Burrows, V., "The impact of a gluten-free diet on adults with coeliac disease: results of a national survey.," *J. Hum. Nutr. Diet.*, 19(1), 41-49, Feb 2006.

[13] Lee A., Newman, J., "Celiac diet: its impact on quality of life," *J. Am. Diet. Assoc.*, 103(11), 1533-1535, Nov 2003.

[14] McElvaney, N.G., Duignan, R., Fielding, J.F., "Coeliac disease: clinical presentations, correlations of dietary compliance, symptomatic response and repeat biopsy findings," *Ulster Med J*, 61(2), 134-138, Oct 1992.

[15] Vahedi, K., Mascart, F., Mary, J.Y., Laberenne, J.E., Bouhnik, Y., Morin, M.C., Ocmant, A., Velly, C., Colombel, J.F., Matuchansky, C., "Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease," *Am J Gastroenterol*, 98(5), 1079-1087, May 2003.

[16] Högberg, L., Grodzinsky, E., Stenhammar, L., "Better Dietary Compliance in Patients with Coeliac Disease Diagnosed in Early Childhood," *Scand. J. Gastroenterol.*, 38(7), 751-754, Jul 2003.

[17] Fabiani, E., Taccari, L.M., Rätsch, I.M., Di Giuseppe, S., Coppa, G.V., Catassi, C., "Compliance with gluten-free diet in adolescents with screening-detected celiac disease: A 5-year follow-up study," *J. Pediatr.*, 136(6), 841-843, Jun. 2000.

[18] Troncone, R., Mayer, M., Spagnuolo, F., Maiuri, L., Greco, L., "Endomysial antibodies as unreliable markers for slight dietary transgressions in adolescents with celiac disease," *J Pediatr Gastroenterol Nutr.*, 21(1), 69-72, Jul 1995.

[19] Sugai, E., Nachman, F., Váquez, H., González, A., Andrenacci, P., Czech, A., Niveloni, S., Mazure, R., Smecuol, E., Cabanne, A., Mauriño, E., Bai, J.C., "Dynamics of celiac disease-specific serology after initiation of a gluten-free diet and use in the assessment of compliance with treatment," *Dig. Liver Dis.*, 42(5), 352-358, May 2010.

[20] Limbach, A., Hoepffner, W., "Verlaufsbeobachtung von Zöliakiepatienten im Kindes-und jungen Erwachsenenalter: latente oder transiente Zöliakie?," *Klin Paediatr*, 215(2), 76-81, Mar-Apr 2003.

[21] Hopman, E.G., von Blomberg, M.E., Batstra, M.R., Morreau, H., Dekker, F.W., Koning, F., Lamers, C.B., Mearin, M.L., "Gluten tolerance in adult patients with celiac disease 20 years after diagnosis?," *Eur J Gastroenterol Hepatol*, 20(5), 423-429, May 2008.

[22] Meuli, R., Pichler, W.J., Gaze, H., Lentze, M.J., "Genetic difference in HLA-DR phenotypes between coeliac disease and transitory gluten intolerance.," *Arch. Dis. Child.*, 72(1), 29-32, Jan 1995.

[23] Bardella, M., Fredella, C., Trovato, C., Ermacora, E., Cavalli, R., Saladino, V., Prampolini, L., "Long-term remission in patients with dermatitis herpetiformis on a normal diet," *Br. J. Dermatol.*, 149(5), 968-971, Nov 2003.